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The Biology of Aging: Current Research and Expected Future Gains

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There has been a very recent surge of interest in research on the biology of aging, particularly regarding its most basic aspects, such as the role of genes in the modulation of life span and the susceptibility to late life disorders. This is graphically illustrated in Figure 1, which contrasts the continuing substantial rate of increase in the scientific literature (Medline) on "genetics and aging" with the recent apparent plateau in the rate of publications dealing with "genetics and birth defects". What accounts for this growing interest by biologists on the nature of aging processes? First of all, powerful new methodologies (Sioud, 2006) have become available that have led to an acceleration of progress in all of the biological sciences. Second, there has been the gradual growth of funding by the National Institute on Aging, established in 1976 with a mandate to include a portfolio of research and training grants on the biology of aging and to provide well standardized resources, such as banks of cells lines and genetically defined strains of rodents free of major infectious agents and with well characterized life tables. This national public effort has been supplemented by non-profit granting agencies dedicated to the advancement of basic research on the biology of aging, notably the American Federation for Aging Research and the Ellison Medical Foundation. Moreover, given the fact that the number one risk factor for most geriatric disorders is biological aging, organizations dedicated to specific late life disorders, such as the Alzheimer's Association, have provided substantial and relevant support for our common mission. Third, scientists have become increasingly aware of the medical, social and economic implications of major demographic shifts towards aging societies within the populations of the developed societies (and, before long, among the developing societies). Fourth, there has been a recent breakthrough in basic research using model organisms that are amenable to genetic analysis and that have comparatively short life spans. This research has provided strong evidence that there exists at least one common biochemical genetic pathway that can be experimentally modified in organisms as diverse as yeast, worms, fruit flies and mice in order to extend both health span and life span [reviewed by (Sinclair & Guarente, 2006)]. That such common "public" mechanisms of aging exist had been suggested by seventy years of research showing that a simple environmental manipulation – dietary restriction – can increase the life spans and health spans of a wide range of organisms (Masoro, 2005). A number of laboratories are now trying to reconcile these two general results. Are they comparable at the cellular and molecular levels of organization?

Biological Conceptions of Aging

Plant biologists often use the term aging to describe *all* changes in structure and function, from birth to death. Most biologists who do research on aging, however, ("biogerontologists") use the term "aging" (or "ageing", if they are British) to refer to the deleterious, non-adaptive changes in structure and function that gradually and insidiously unfold soon after the peak of reproductive activity. This is not to say that how an organism develops has nothing to do with how an organism ages. Clearly, how well an organism is built will have a lot to do with how long it continues to function well. It is also apparent that not *every* change in structure and function is deleterious; some are adaptive compensations, including alterations in behavior (Martin, 1997). The timing of these various life history events is best understood by evolutionary biological theory (Austad, 1997; Rose, 1991). Species that evolve in ecological settings that are extremely hazardous (e.g., numerous predators, uncertain food and water supplies, harsh changes in climate, dangerous terrains and potentially lethal infectious agents and their vectors) have to "get the job done fast". That job, of course, is reproduction. Such species therefore can be expected to have rapid rates of development with early sexual maturity and numerous progeny over a comparatively short period of time. Given such a scenario, there is no selective pressure for nature to invent enhanced mechanisms to ensure long periods of robustness. The energetic expense account is better used for reproduction. "Good" varieties of genes (alleles) will appear by mutation from time to time, but given the age-structured populations of most animal species, any allele that may have contributed to the enhancement of late life survival of a rare individual will have had little chance of contributing significantly to the subsequent generations, as these genes will have been diluted by the vastly more common alleles in the general population dominated by the younger cohorts. "genes diluted"? The same would of course be true of any "bad" gene that did not reach some threshold of phenotypic effect until comparatively late in the life span; nature would have little opportunity to select against such genes – hence the difficulty of purging populations from such mutations as those associated with diseases such as Huntington's disease. Given changing ecologies, different life history trajectories can be expected to evolve. There is experimental evidence to support that conjecture, given certain conditions (Austad, 1993). There have been a number of challenges to the overall picture we have presented. For example, some species of fish continue to enjoy apparently indefinite growth (Patnaik et al., 1994). As such, they would be expected to be more resistant to predators as they age. The patterns of selection with age are therefore likely to be quite unusual (Baudisch, 2005). Some anthropologists and economists, as well as most laymen, will argue that genes are indeed selected in grandparents who provide support for their children and grandchildren (Kaplan & Robson, 2002; Lee, 2003). There is no denying that this has occurred in modern times, and that it might be debatable measurable in contemporary "primitive" tribes, but we are the result of natural selection that produced our species long ago, at a time when very few grandparents will have survived. ~~There is~~ one aspect of the biology of aging ~~that~~ is clear to all biogerontologists, however, – the enormous plasticity of life spans and, by inference, intrinsic rates of aging. Among mammals, typical strains of laboratory mice live for up to 3-4 years, while some species of whales, as judged by indirect chemical assays, can survive for over 200 years (George et al., 1999). Such plasticity provides a degree of optimism for the potential to intervene in processes of aging. As we shall see below, however, there are also a large number of "private" mechanisms of aging, mechanisms that apply to particular individuals or pedigrees. This is particularly apparent in our own species, which is subject to considerable variation in its genetics and environment. It is also apparent that "lady luck" plays a large role in how we age, as we shall see.

The Roles of Nature, Nurture and Chance in Longevity

Studies of the longevities of human twins, particularly those in the Scandinavian countries, have provided estimates of the role of heredity. Readers may be surprised that genes explain only about a quarter to a third of the variability in longevity within our species [reviewed by (Finch & Tanzi, 1997)]. We do not know how much of the residual variation is due to chance events and how much is due to environmental impacts. Research with model organisms lead us to suspect that chance events have the largest impact, however. *Caenorhabditis elegans*, a round worm, provides a robust example. Laboratory isolates of these worms are genetically identical and they can be aged under exceedingly well controlled environments (suspension cultures free of bacteria). Despite this excellent control of genes and environment, numerous experiments have documented enormous variability in how long such worms can live (Vanfleteren et al., 1998). The same phenomena have been repeatedly observed for inbred strains of fruit flies, mice, rats, hamsters and other species. Some recent research hints at an important role for random changes in the regulation of gene expression, presumably related to chemical modifications that are "on top of" the genetic material (Rea et al., 2005). These were originally referred to as "epinucleic" events (Lederberg, 1958), but are now usually referred to as "epigenetic" alterations. There is no doubt, however, that environmental agents can greatly impact ~~upon~~ the pace of aging, at least for some aspects of aging. The best example is cigarette smoke, which has deleterious effects upon virtually all body systems (Bernhard et al., 2006). Cigarette smoke contains about 4,000 chemical agents, including numerous carcinogenic substances (Burns, 1991). Many of these compounds cause gene mutations, but here too one sees a role for chance events. One may have two genetically identical individuals with comparable exposures to mutagenic substances, but the genome of one may sustain "hits" in varieties of genes that are keys to the development of cancers, while the other may sustain most of the "hits" in less important segments of DNA, such as pseudogenes.

Classes of Gene Action That Modulate Rates of Aging

are any of these anti-mutagenic?

The evolutionary theory of *why* we age, briefly referred to above, provides guides to *how* we age. One group of such gene actions has been referred to as "longevity assurance genes" (Hodes et al., 1996). They include the more numerous genes involved in the repair of damaged DNA and the protection of macromolecules from oxidative damage. The latter class of genes is relevant to what is arguably the leading current hypothesis for how we age – the accumulation of oxidatively altered proteins, lipids, DNA and RNA, particularly those found within mitochondria, the cell organelle that generates the major flux of reactive oxygen species (Wallace, 2005). A second major class of gene action responsible for senescent phenotypes is referred to as "antagonistic pleiotropy" (Rose, 1991; Williams, 1957). This refers to a situation in which a variety of gene, while selected because of its beneficial effect upon the organism during the early stages of its life history, has bad effects late in the life course. One example that is often cited by biogerontologists relates to the observation that many types of human cells gradually lose the ability to replicate because the enzyme (telomerase) that is necessary to copy terminal portions of the chromosomes (telomeres) is greatly down-regulated in the course of early development (Shay & Wright, 2000). This is thought to have evolved as a mechanism for the suppression of cancers during the early period of life. Late in life, however, when fully replicatively senescent cells begin to accumulate in tissues, they can have the paradoxical effect of contributing to tumor progression as a result of factors secreted by these cells that change the properties of the connective tissues and stimulate the growth of nearby epithelial cells (Campisi, 2005). There is now good evidence that replicatively senescent cells do indeed accumulate in the skin of aging primates and that these cells show foci of DNA damage (Jeyapalan et al., 2006). A third class of gene action predicted by the evolutionary theory, referred to as "mutation accumulation" (Medawar, 1957), involves mutations whose phenotypic effects do not reach a significant threshold until after the peak of reproduction, when physiological assays show declines in function of many body systems. Nature therefore cannot effectively select against such mutations and they can accumulate in certain pedigrees, creating the "private" mechanisms of aging referred to above. While individually rare, there are potentially vast numbers of such mutations. Three such genetic loci have already been documented as bearing dominant mutations leading to Alzheimer's disease [reviewed by (Tanzi & Bertram, 2005)]. Although referred to as "early onset" cases, these forms of dementia typically unfold in late middle age, and thus usually will have escaped the force of natural selection. Recent research has revealed a growing list of genes, mutation at which can lead to forms of Parkinson's disease (Hardy et al., 2006).

What the Future Holds

For the immediate future, given the very recent decline in research funding by the National Institutes of Health (Zerhouni, 2006), the pace of biomedical research may well decline somewhat and we may lose young investigators to other occupations. This is quite unfortunate, as the opportunities for progress have been growing exponentially, as evidenced, for example, by the data of Figure 1. Extraordinary claims have been made by some scientists suggesting that we are now close to the stage of engineering very substantial enhancements of life spans and health spans (de Grey, 2005). Most biogerontologists do not agree with such claims, given the fact that we remain ignorant of the detailed mechanisms of aging. Moreover, interventions typically come with tradeoffs. For example, let's assume that it will be possible in the not too distant future to develop drugs that mimic the effects of dietary restriction in rodents. First of all, we do not yet know if dietary restriction will have comparable effects in human subjects. Second, given the marked genetic heterogeneity of our species, there is likely to be substantial variability in the response to any such intervention ("one man's meat is another man's poison"). Third, not all subjects will be happy about a tradeoff that involves a decrease or cessation of reproduction or a possible effect upon libido. Nevertheless, there are some encouraging developments that could lead to interventions in particularly susceptible individuals. There is, for example, considerable interest in a recent publication indicating that large doses of a polyphenolic compound found in red wine (resveratrol, trans-3,5,4'-trihydroxystilbene) can normalize the patterns of gene expression, improve the insulin sensitivities and increase the life spans of overfed, obese mice (Baur et al., 2006). At least one biotechnology company is said to be now actively pursuing the synthesis of related compounds that might have greater specific activities. Meanwhile, we do not recommend drinking the number of glasses of red wine (~300 per day) needed to match the dose used in these experiments with mice!

and perhaps vice versa

of resveratrol

There is also reason to celebrate the emergence of the field of "regenerative medicine". A particularly exciting recent finding has been the observation that the defects in the repair of skeletal muscles of old mice are not due to a deficiency of muscle satellite cells (the stem cells of skeletal muscle). Instead, it appears to be due to a deficiency in the microenvironments of such cells. The deficiency could be corrected by a circulating factor or factors found in young animals (Conboy et al., 2005). The implications for therapy are substantial, particularly if this obtains for many types of stem cells, as one might be able to develop small molecular weight compounds that could "awaken" the stem cells in older individuals.

Conclusions

We can conclude that there has been striking progress in our understanding of basic mechanisms of aging, but that we still a long way from applying this knowledge for the "engineering" of unusually long and healthy life spans. There are both common ("public") and unusual ("private") ways to age. Any future attempts at intervention will have to take this into account.

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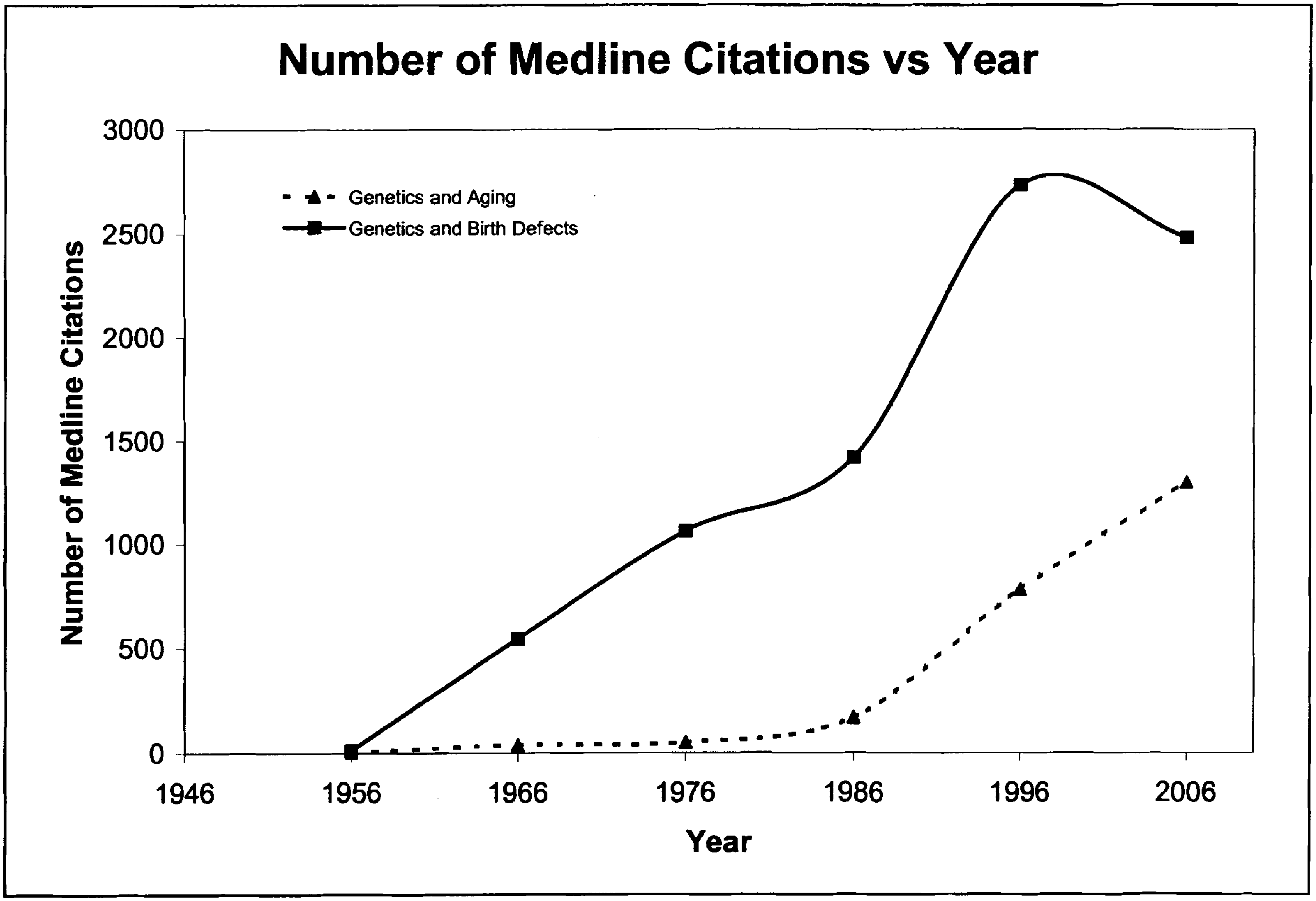
Number of Medline Citations vs Year
Number of Medline Citations
Year
Genetics and Aging
Genetics and Birth Defects
3000
2500
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